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Versatile exposure system for laboratory experiments finalized to therapeutic applications in the IF range

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Abstract

Several nanotechnologies rely on the use of magnetic field for therapeutic purposes, as cancer treatment, inflammation, and diseases of the nervous system. The liposomal drug delivery system is a novel technique that allows a controlled release of drugs encapsulated in a nano-carrier (i.e. liposomes), by the application of an external (electric, magnetic, thermal) stimulus to guarantee a local effect on the region where the disease has developed. Another interesting application of magnetic field is the transcranial magnetic stimulation, which is used to the study and treatment of a wide variety of neurologic and psychiatric conditions.
In this paper, an analytical analysis and a numeric modelling approach is reported for the design of a versatile magnetic exposure system, suitable for different applications: *in vitro* magnetoliposomes (vesicles containing super-paramagnetic iron oxide nanoparticles) drug delivery, and *in vitro* studies to understand the action of magnetic stimulation on neurons. The simulation shows that the system is able to generate intensities of the order of mT, in a frequency range up to 20 kHz, without causing secondary effects such as a local thermal increase.

1. Introduction

The technological progress has increased the use of magnetic field as external stimulus for the therapy of inflammatory diseases, the treatment of neurologic disorders, and for drug delivery [1,2]. Stimuli-response release of a drug from nano-carriers at a specific time and location are major targets of drug delivery research. Generally, drug release is obtained by changing environmental condition (pH, temperature, ultrasound) [3,4], and integrated control release has been approached by combining temperature and magnetic fields as triggering agents, using magnetoliposomes (MLs, vesicles containing super-paramagnetic iron oxide nanoparticles) as nanocarriers [5,6].
Furthermore, some studies suggested that magnetic fields at low intensities are a good trigger to control the releasing of the drugs [7,8,9]. The idea is to induce a mechanical stress on the liposome membrane, due to nanoparticles oscillations, in order to obtain the drug release. The aim is to obtain therapeutic efficacy without a thermal effect, which can create considerable discomfort during the treatment.
Other important applications of magnetic fields are non-invasive stimulation of the central nervous system, such as transcranial magnetic stimulation (TMS) [9] or low-intensity pulsed magnetic field stimulation [10]. In this context, *in vitro* studies are necessary to understand the action on neuronal structures [10].
The aim of this paper was to design a versatile magnetic exposure system, which can be used for *in vitro* studies such as Mls drug delivery and magnetic stimulation of neuronal structures. The study has been carried out both analytically and numerically, using the Sim4Life software. First, the system, consisting of two squared Helmholtz coils, has been simulated to verify the matching of project parameters (magnetic field intensity in the order of mT, in a frequency range up to 20 kHz). Next, for the Mls drug delivery model, we placed a cuvette, filled with a conductive solution (0.049 S/m, experimentally measured), at the center between the two coils. Finally, to test the system for neuronal magnetic stimulation *in vitro* applications, a chamber typically used to investigate brain slices, filled with artificial cerebrospinal fluid, has been simulated between the two Helmholtz coils. For both exposure systems, the aim was to perform a dose-dependent analysis of possible secondary effect arising in the samples, due to the magnetic field application.

2. Materials and Methods

To project our multipurpose magnetic exposure system, a first analytical study was performed through the equation of standard Helmholtz coils, dimensioning coil geometry and shape, coil thickness, number of wires, in order to have an exposure system that could generate a magnetic field

with intensity of mT and in a wide frequency range (up to 20 kHz).
To validate the chosen parameters, numerical simulations were performed using the Software Sim4life 2.1 in the frequency domain using the quasi magneto-static module. Sim4Life software is an interactive environment for modelling and simulating scientific and engineering problems. Regarding the exposure system for *in vitro* MIs drug delivery applications, the simulation has been carried out considering a frequency of 20 kHz (experimental frequency). For the *in vitro* exposure system, simulations have been done at the frequency of 3 kHz, typically used in TMS applications [11].

3. Results and Discussion

The aim of this paper was to perform a dose-dependent analysis with a magnetic field exposure in the range of mT and in a frequency range up to 20 kHz. From the analytical study, coil dimensions of 15 cm of diameter and a thickness of 0.85 cm were identified with 200 wires, in order to have a magnetic field intensity close to 2 mT, with a current of 0.6 A. Based on the chosen parameters, numerical simulations were performed.
The coils geometry is shown in Fig. 1. Two squared coils have been simulated as current wire of 15 cm, placed at 7.5 cm of distance between each other. Due to the impossibility to give a thickness to the coil wire within the used simulation software, we supplied the two coils with a current of 120 A (0.6 A per 200 number of wires). The coils are parallel to the xy plane (Fig. 1) so that the magnetic field results applied along the z-axis.

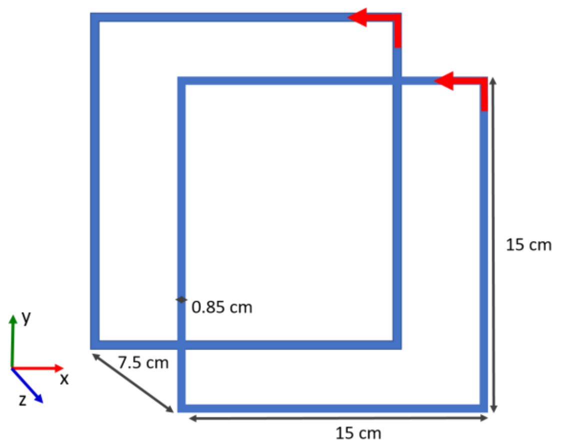

Figure 1. Two squared Helmholtz coils of 15 cm of dimension, placed at 7.5 cm of distance. The thickness is of 0.85 cm.

The simulations were implemented using a fine mesh with the magneto-quasi static module. In Fig. 2 the magnetic flux density along the x (upper panel) and z axis (lower panel) is reported at the frequency of 20 kHz. It can be noticed that at the center of the exposure system, where the samples are supposed to be placed, the intensity of the magnetic field is uniform with an intensity around 1.45 mT.

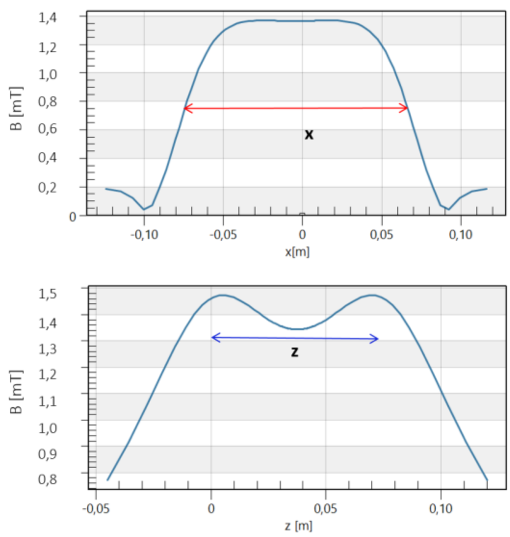

Figure 2. The magnetic flux density is reported along the x (upper panel) and z plane (lower panel). A good homogeneity of the B field is reached with an intensity of 1.4 mT.

This result is also confirmed from the study of the magnetic field uniformity in the volume between the coils. In Table 1 it is possible to notice a homogeneity of the magnetic field of 95 % in the exposure volume of 9.12 x 9.12 x 7.5 cm^3.

Table 1. Magnetic field homogeneity values for different volume of exposure.

Magnetic field homogeneity			
	95 %	**90 %**	**80 %**
Δx [cm]	9.12	10.36	11.86
Δy [cm]	9.12	10.36	11.86
Δz [cm]	7.49	8.98	11.60
Useful volume [cm^3]	622.97	963.82	1631.65

The MIs exposure system is presented in Fig. 3. The cuvette is simulated as a cylinder of 7.5 cm of height and 0.6 cm of radius, for half is filled with a conductive solution with σ=0.049 S/m, which represents the conductivity of MIs solution experimentally measured (data not shown).

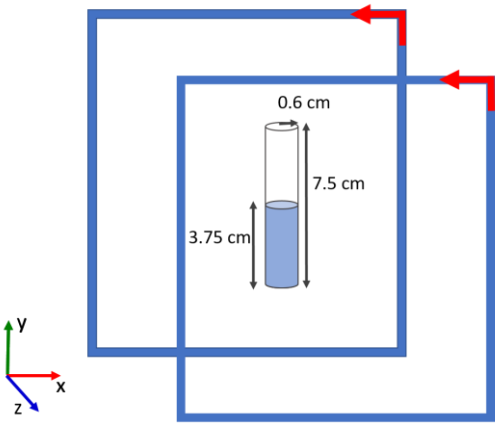

Figure 3. Two squared Helmholtz coils of 15 cm of dimension, placed at 7.5 cm of distance. The cuvette (7.5 cm of height) is filled for half of its dimension with a conductive solution.

In Figure 4 the magnetic field density is reported on the liposomes solution.

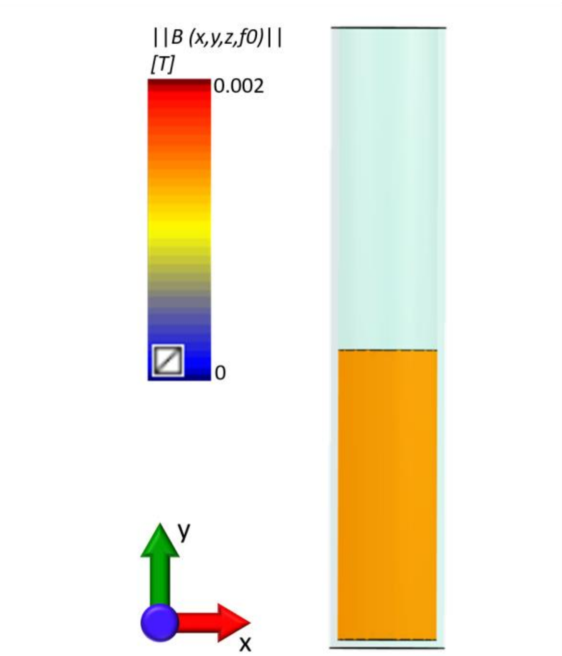

Figure 4. Magnetic field density on the solution surface

It is possible to see that the magnetic field is completely uniform with an intensity of 1.45 mT. In Figure 5, the electric field (E) trend is reported inside the exposed solution along the x (upper panel) and y axis (lower panel), respectively. It can be noticed how, in the middle of the sample, the value is very low (below 1 V/m), suggesting no significant induced electric field.

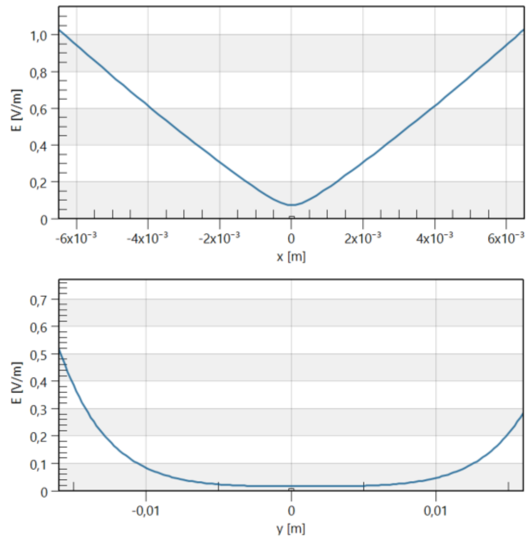

Figure 5. Electric field (E) trend in the solution region along the x (upper panel) and y-axis (lower panel). The E field values are below 1 V/m.

Concerning the simulations for the *in vitro* exposure system, we modelled a chamber of plexiglass, like the ones typically used in neurophysiological studies on brain slices, placed between the two coils (Fig. 6), filled with the artificial cerebrospinal fluid solution where the brain slices are supposed to be exposed (yellow region in Fig. 6).

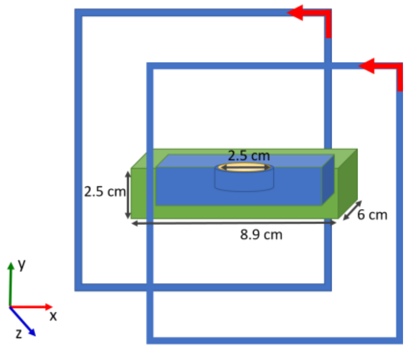

Figure 6. Simplified draw of the chamber of 8.9 x 6 x 2.5 cm^3 volume placed at the center of the two coils. In yellow, the space in which is supposed to be placed the slice. In blue, the artificial cerebrospinal fluid solution.

The magnetic field distribution results to be homogeneous in all the exposure volume as for the other cases (data not showed). In Fig. 7 the electric field E (upper panel) and the current density J (lower panel) are reported along the x axis in the volume used for the slice exposure. The E field results to be very low, with intensities in the order of 50 mV/m, and uniform. The same homogeneity has been achieved for the current density with values up to 0.16 A/m^2. For both the electric field and the current density generated inside the exposed solution, we can conclude that secondary effects due to the magnetic field application can be excluded, because of the low intensities involved.

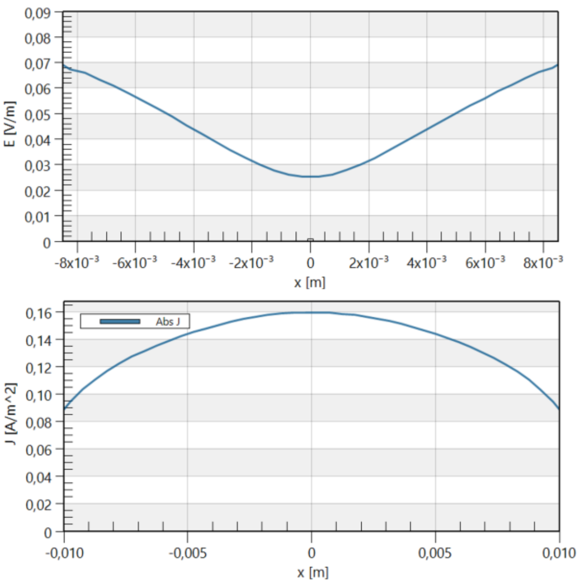

Figure 7. Electric field (E) (upper panel) and current density (J) (lower panel) along the x-axis inside the chamber exposure volume.

4. Conclusions

The goal of the present study was the design of a multipurpose exposure setup, for *in vitro* applications as MLs poration for drug delivery, and for magnetic neuronal stimulation. We performed a dose-dependent analysis for both applications, to verify if it was possible to obtain a magnetic field intensity in the order of mT with no secondary effect on the exposed sample, such as a thermal increase due to high induced electric field or current density. Thanks to an analytical and numerical study, the system was designed as two squared Helmholtz coils with 15 cm of side, able to generate a magnetic field of 1.45 mT in the volume of exposure with a homogeneity of 95%. For both MLs delivery system and the *in vitro* chamber, no significant values of E and J have been induced in the exposed solution. Thus, the simulation shows that the system gives the possibility to apply a magnetic field in the order of mT avoiding a thermal increase in a frequency range up to 20 kHz.

5. References

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